ORIGINAL ARTICLE

Metabolic Activity of the Tongue in Obstructive Sleep Apnea

A Novel Application of FDG Positron Emission Tomography Imaging

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Abstract

Rationale: The metabolic activity of the tongue is unknown in patients with obstructive sleep apnea (OSA). Tongue electromyographic (EMG) activity is increased in patients with OSA. This increase in tongue EMG activity is thought to be related to either increased neuromuscular compensation or denervation with subsequent reinnervation of the muscle fibers. Increased glucose uptake in the tongue would support increased neuromuscular compensation, whereas decreased glucose uptake in the tongue would support denervation with subsequent reinnervation of the muscle fibers.

Objectives: To investigate the metabolic activity of the genioglossus and control upper airway muscles in obese patients with sleep apnea compared with obese control subjects.

Methods: Obese subjects with and without OSA underwent a standard overnight sleep study to determine an apnea–hypopnea index. Each subject had a positron emission tomography with [^{18}F]-2-fluoro-2-deoxy-D-glucose scan in addition to noncontrast computed tomography or magnetic resonance imaging. Glucose uptake was quantified within upper airway tissues with the standardized uptake value.

Measurements and Main Results: We recruited 30 obese control subjects (apnea–hypopnea index, 4.7 $\pm$ 3.1 events per hour) and 72 obese patients with sleep apnea (apnea–hypopnea index, 43.5 $\pm$ 28.0 events per hour). Independent of age, body mass index, sex, and race, patients with OSA had significantly reduced glucose uptake in the genioglossus ($P = 0.03$) in comparison with obese normal subjects. No differences in standardized uptake value were found in the control muscles (masseter [$P = 0.38$] and pterygoid [$P = 0.70$]) and subcutaneous fat deposits (neck [$P = 0.44$] and submental [$P = 0.95$]) between patients with OSA and control subjects.

Conclusions: There was significantly reduced glucose uptake in the genioglossus of patients with sleep apnea in comparison with obese normal subjects with [^{18}F]-2-fluoro-2-deoxy-D-glucose positron emission tomography imaging. The reduction in glucose uptake was likely secondary to alterations in tongue muscle fiber-type or secondary to chronic denervation. The reduced glucose uptake argues against the neuromuscular compensation hypothesis explaining the increase in tongue EMG activity in obese patients with OSA.

Keywords: FDG-PET; genioglossus; masseter; obstructive sleep apnea; MRI

The prevalence of obstructive sleep apnea (OSA) is reaching epidemic proportions (1, 2) and is independently linked to cardiovascular disease (3, 4) and mortality (5). Imaging studies have shown that the volume of the tongue is enlarged in patients with sleep apnea (6). The tongue is thought to be the primary upper airway pharyngeal dilator muscle (7). However, very little is known about the metabolic activity of the tongue or other upper airway muscles.

OSA has both an anatomic and neural component in its pathogenesis (6, 7). The upper airway is narrowed, even during

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At a Glance Commentary

Scientific Knowledge on the Subject: This study investigates the abnormalities in glucose uptake by the primary dilator muscle of the upper airway (genioglossus) using positron emission tomography scanning in patients with obstructive sleep apnea (OSA) and obese control subjects. Our data indicate that the metabolic activity (glucose uptake) of the genioglossus is reduced in patients with OSA compared with obese control subjects without sleep apnea.

What This Study Adds to the Field: This is the first study examining metabolic activity of the tongue in patients with OSA. We have shown reduced metabolic activity of the tongue in patients with OSA, and this imaging modality offers a new paradigm for understanding the muscle properties of the upper airway soft tissue structures. The reduced glucose uptake argues against the neuromuscular compensation hypothesis explaining the increase in tongue electromyographic activity in patients with OSA.

wakefulness, in patients with OSA, as revealed by imaging studies (6, 7). It is proposed that there is increased activation of upper airway dilator muscles during wakefulness to compensate for this airway narrowing and the increased collapsibility of the upper airway in patients with sleep apnea (the neuromuscular compensation hypothesis) (7–9). This concept is supported by the observation that patients with sleep apnea have increased compound electromyographic (EMG) activity of the genioglossus compared with control subjects (7–12). If so, then patients with OSA should have increased metabolic activity of their tongue muscle during wakefulness compared with control subjects, after controlling for confounding variables, such as obesity, sex, race, and age.

There is, however, an alternative explanation for the increase in compound EMG activity. Upper airway vibration during apneic events and snoring can lead to denervation with subsequent reinnervation of muscle fibers in upper airway dilator muscles (13, 14). Reinnervation leads to an increase in amplitude of action potentials of reinnervated muscle fibers (15) that also results in an increase in the compound EMG. Recent data, recording activity of individual muscle fibers in the genioglossus, indicate that the amplitude of action potentials is indeed increased in the tongue of patients with sleep apnea compared with control subjects (10, 16, 17). If denervation occurs, it would be expected to decrease rather than increase metabolic activity of the tongue. Interruption of nerve supply to skeletal muscle results in the development of insulin resistance in the affected muscle (18). This insulin resistance is characterized by a decreased ability of insulin to stimulate transport of sugars, glycogen synthesis, and amino acid transport in the denervated muscles (18, 19).

Metabolic activity of muscle is also affected by fiber type (20–23). Studies of the genioglossus (24) have shown that patients with OSA have an increased percentage of type II muscle fibers in comparison with control subjects (25). Type II muscle fibers, in contrast to type I fibers, are known to have less overall glucose uptake (20–23, 26) and be less resistant to fatigue (8).

Altered composition of muscle also alters its metabolic activity. Autopsy (27) and magnetic resonance imaging (MRI) (28) studies in normal subjects have demonstrated that the human tongue has a high percentage of intramuscular fat. Recent studies have also shown that the tongue (29) has increased fat deposition in patients with sleep apnea in comparison with control subjects. Adipose tissue (30) is known to have less glucose uptake than muscular tissue (31, 32). Thus, adipose tissue in the tongue may contribute to a reduction in the metabolic activity of the tongue.

It is possible to assess metabolic activity of the tongue *in vivo* by using positron emission tomography (PET) with [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG). This imaging modality offers the unique ability to map glucose metabolism in tissue-specific regions (33, 34). FDG is a glucose analog that can be used to quantify glucose uptake. PET, when used in tandem with computed tomography (CT) and MRI (Figure 1), allows for more precise anatomic localization of radiotracer uptake (35, 36). We therefore performed MRI in the same subjects, including Dixon imaging (37, 38), to assess fat deposition in the tongue and relate this to our findings with PET imaging.

Using this analytical imaging modality, we investigated whether patients with OSA have altered metabolic activity in the genioglossus and control upper airway muscles compared with subjects without OSA. The neuromuscular-compensation hypothesis would predict an increase in metabolic activity of the tongue, whereas if there is muscle injury and remodeling, metabolic activity should decrease. This study provides a novel paradigm for examining the metabolic properties of

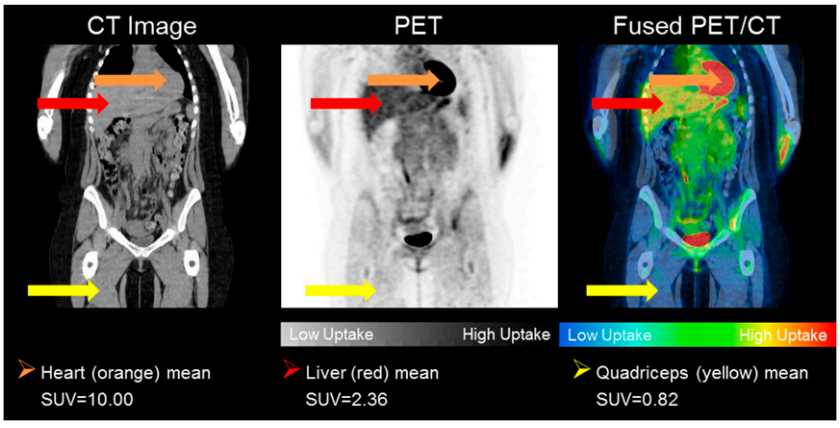

Figure 1. Representative computed tomography (CT), positron emission tomography (PET), and fused PET-CT images of the entire body. Color bars below PET and fused PET-CT image indicate high uptake (*black*, *red*) and low/no uptake (*white*, *blue*). Heart (*orange arrow*) has relatively high standardized uptake value (SUV), whereas liver (*red arrow*) and resting quadriceps muscle (*yellow arrow*) have significantly lower SUV.

these upper airway dilator muscles. We used a case-control design to examine our *a priori* hypotheses that glucose metabolism is decreased in the genioglossus of patients with sleep apnea in comparison with obese control subjects; and there are no differences in glucose uptake in the control muscles (masseter and pterygoid) and subcutaneous fat deposits (neck and submental) of the upper airway between patients with OSA and control subjects. Portions of this investigation have been previously presented in abstract form (39).

Methods

Subjects

The present study used a case-control design in obese patients with sleep apnea and control subjects. The University of Pennsylvania (Philadelphia, PA) institutional review board for human studies approved the protocol (IRB protocol number, 808496), and informed written consent was obtained from each subject. In addition, the study was reviewed and approved by the Radioactive Drug Research Committee at the University of Pennsylvania. Cases (apnea-hypopnea index [AHI] $\geq$15 events per hour) were recruited primarily from the Center for Sleep and Circadian Neurobiology (Philadelphia, PA). Control subjects (AHI $\leq$10 events per hour) were recruited from the Philadelphia area.

Polysomnography

Standard polysomnography techniques were performed as described in our previous studies (6). *See* the online supplement for scoring definitions.

FDG-PET Imaging

FDG-PET images were acquired on either a dedicated PET (Allegro; Philips Healthcare, Best, The Netherlands) or PET-CT scanner (Gemini TF; Philips Healthcare). We followed the routine PET clinical protocol, which required subjects to fast greater than or equal to 6 hours before their scan and PET imaging was initiated 60 minutes postintravenous injection of FDG. Subjects were given instructions during the PET scan but never spoke. They were instructed not to respond and did not talk during the uptake time or during the scanning. If the subjects were too heavy to fit on the Allegro scanner (just PET scanning not PET-CT), their PET scans were conducted on the Gemini TF scanner (PET-CT). *See* the online supplement for further details about the PET imaging protocol.

As mentioned, we used two different PET scanners, one of which had the ability to acquire simultaneous PET-CT images. The first PET-CT was validated at the University of Pennsylvania (many years ago) by comparing the images from PET-CT with those of Allegro (PET only) and there was an excellent agreement between the two for both the quality of the scans and for the standardized uptake value (SUV) measurement. Thus, the SUV measurements would be equivalent whether they were performed on the PET-only scan or PET-CT scan. The PET-only scanner (Allegro) was used as the primary scanner and the analysis was completed by fusing PET-MRI. When the availability of the Allegro was limited or when subjects were too heavy to fit on the Allegro scanner, their PET scans were acquired on the Gemini TF PET-CT scanner. The analysis in these subjects was completed by fusing PET with low-dose CT images. Because all subjects had an MRI of their upper airway, we were able to compare analyses completed using both fused PET-CT and fused PET-MRI within the same subjects. We analyzed 10 subjects with PET, CT, and MRI and found excellent agreement between the SUVs obtained from PET-CT images and PET-MRI (intraclass correlation coefficient, >0.95). Thus, we are not concerned about any potential biases resulting from performing the image analysis using PET-CT or PET-MRI.

CT and MRI

Low-dose CT images (when used) and MRIs were coregistered with FDG-PET scans in the axial, sagittal, and coronal planes for precise anatomic localization of FDG uptake. Low-dose noncontrast CT images with 4-mm slice thickness were acquired from the hard palate to the larynx. When CT scans were not used, we used the MRI to coregister with the PET images (Figures 1, 2A, and 2B). *See* the online supplement for MRI sequences including the Dixon imaging for fat.

Measurement of Glucose Uptake in Upper Airway Soft Tissue Structures

The conventional metric to analyze glucose metabolism in tissue-specific regions is the mean SUV, a unit-less quantitative measure of glucose uptake (Figure 1) (31). The SUV is defined as the uptake activity per gram of tissue divided by the injected activity per kilogram of body weight (40). To determine the SUV of the upper airway

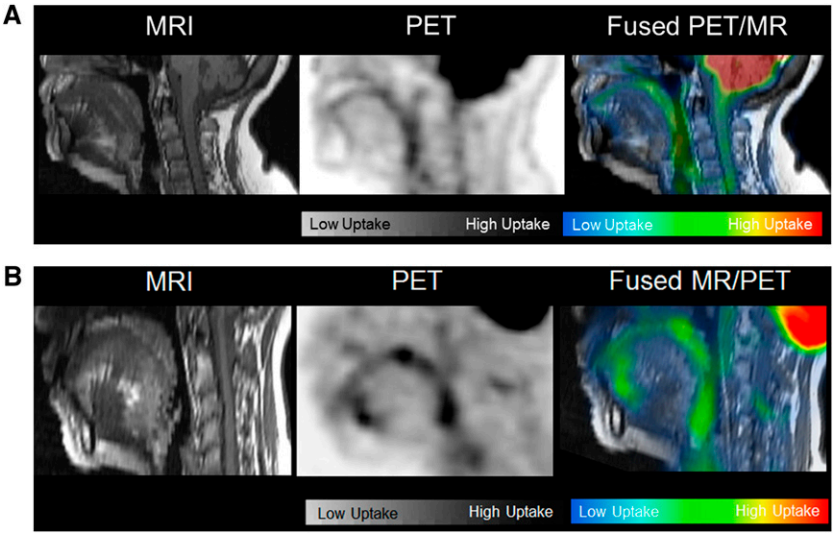

Figure 2. (*A*) Representative magnetic resonance imaging (MRI), positron emission tomography (PET), and fused PET-MRI of the upper airway in a patient with sleep apnea. Color bars below the PET and fused MRI-PET image indicate high uptake (*black*, *red*) and low/no uptake (*white*, *blue*). (*B*) Representative MRI, PET, and fused PET-MRI of the upper airway in control subject. Color bars below the PET and fused MRI-PET image indicate high uptake (*black*, *red*) and low/no uptake (*white*, *blue*).

soft tissue structures (tongue, masseter, pterygoid, neck, and submental subcutaneous fat deposits), we placed a region of interest at the core of each soft tissue. Using dedicated software (AquariusNet Viewer; TeraRecon, Foster City, CA), we fused PET and CT-MRI (Figures 2A and 2B). *See* the online supplement for placement of regions of interest using the dedicated software.

Quantification of Intramuscular Fat in the Tongue

Intramuscular tongue fat was quantified with Dixon imaging. All subjects underwent MRI of the upper airway. The tongue was subdivided into eight regions: four within the retropalatal (RP) and four within the retroglossal (RG), using standard T1 spin echo axial and Dixon water-suppressed images (29). *See* the online supplement for further details of the MRI fat sequence.

Reliability Analysis of Measurements

Reproducibility of the SUV analysis was assessed by completing 10 full analyses of randomized subjects on two separate occasions (same images analyzed at two different time points). Ten subjects were additionally analyzed using PET images fused with CT images and then with MRIs to test for agreement in SUV measurements based on anatomic localization using these two different structural imaging modalities (*see* comments above).

Statistical Analysis

Continuous variables were summarized using means and standard deviations and categorical variables using frequencies and percentages. Chi-square tests and *t* tests examined differences in demographics and soft tissue SUVs between apneic and control groups. To assess whether there were differences between patients with OSA and control subjects after adjustment for covariates, we used multivariate linear regression, with case-control status as a predictor variable. Adjusted linear associations of soft tissue SUVs on obesity and tongue fat measures were examined using Pearson correlations. Analyses were adjusted for *a priori* known covariates, including age, body mass index (BMI), sex, and race. In addition, to control for imbalances in these covariates, we performed a secondary analysis within a subsample of case-control pairs matched on race, sex, age (within 10 yr), and BMI (within 5 kg/m^2). A P less than 0.05 was considered significant for our primary analyses. Given this level of significance, our sample size for our primary analyses (72 patients with sleep apnea, 30 control subjects) resulted in 85% power to detect a significant mean difference in SUV of approximately 0.65 standard deviations in our *t* test analyses. Similarly, we have 85% power to detect a significant association in our analysis or covariance models if case-control status explains 7% of the variability in SUV (i.e., $R^2 = 0.07$), which reflects a small to moderate effect size (41). Analyses were performed using Stata 12 (StataCorp. 2011. Stata Statistical Software: Release 12; StataCorp LP, College Station, TX) and SAS Version 9.3 (SAS Institute, Cary, NC). Additional statistical methods are presented in the online supplement.

Results

Our study was comprised of 72 OSA cases (AHI $\geqslant$15) and 30 obese control subjects with AHI less than or equal to 10 events per hour. Patients with OSA had a mean $\pm$ SD AHI of 43.5 $\pm$ 28.0 events per hour and control subjects had an AHI of 4.7 $\pm$ 3.1 (Table 1). Both patients with OSA and control subjects were obese, but cases were heavier (BMI of 40.4 $\pm$ 7.7 vs. 35.5 $\pm$ 6.0; $P = 0.003$). However, there was reasonable overlap in distribution of BMI between groups (*see* Figure E5 in the online supplement), allowing for statistical adjustment. Cases were also older ($P < 0.001$) and more likely to be male ($P = 0.030$). There was no significant difference in race between patients with sleep apnea and control subjects ($P = 0.138$).

Metabolic Activity of Upper Airway Soft Tissue Structures

Reliability of PET measurements. The objective of this study was to investigate the metabolic activity (glucose uptake) in the genioglossus and surrounding upper airway control muscles in obese patients with sleep apnea compared with obese control subjects. Intraclass correlation coefficients in our repeat analyses for mean soft tissue SUV analysis (genioglossus, masseter muscle, pterygoid muscle, neck fat, and submental fat) were greater than 0.95, indicating a highly reproducible analysis. Moreover, intraclass correlation coefficients for SUV analyses completed using PET images fused with CT and MRI were greater than 0.95, indicating that SUVs obtained from region of interest placement based on fused PET-CT images were no different from those obtained from region of interest placement based on fused PET-MRI. Forty-seven subjects were analyzed using fused PET-CT images and 55 subjects using fused PET-MRI.

Differences in the SUV of the upper airway structures between patients with sleep apnea and control subjects. A representative patient with sleep apnea is shown to have reduced FDG uptake in the genioglossus in comparison with a control subject (Figure 3). In all subjects, the mean SUV of the tongue was significantly lower in patients with OSA compared with control subjects (1.28 $\pm$ 0.20 vs. 1.41 $\pm$ 0.31; $P = 0.048$) before covariate adjustment (Table 2). After adjusting for age, BMI, sex, and race, this difference remained significant ($P = 0.030$). We also observed a significant reduction for the SUV of the middle slice (the middle slice has less tongue fat than the other slices) of the

Table 1: Demographics of the Study Sample

Characteristic	Patients with Sleep Apnea (*n = 72*)	Control Subjects (*n = 30*)	*P* Value*
Age, yr	49.3 $\pm$ 12.0	37.9 $\pm$ 11.9	**<0.001**
BMI, kg/m^2	40.4 $\pm$ 7.7	35.5 $\pm$ 6.0	**0.003**
AHI, events per hour	43.5 $\pm$ 28.0	4.7 $\pm$ 3.1	**<0.001**
Sex, M:F	36:36	8:22	**0.030**
Race, W:AA	34:38	19:11	0.138

Definition of abbreviations: AA = African American; AHI = apnea–hypopnea index; BMI = body mass index; W = white.
Significant differences ($P < 0.05$) are presented in bold.
*P value from *t* test or chi-square test.

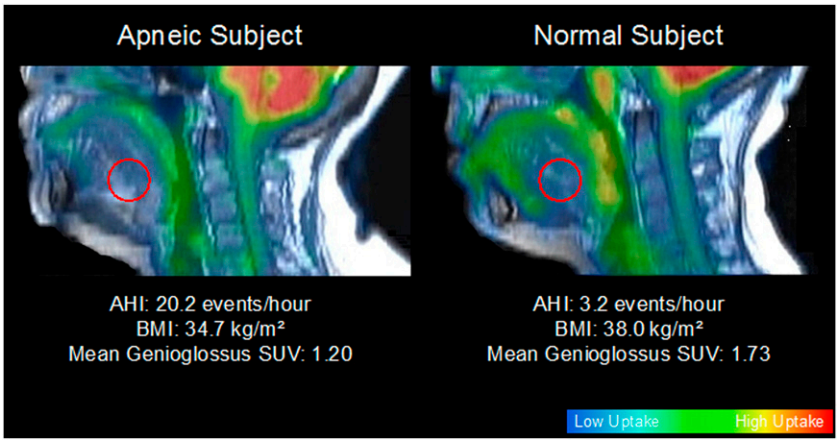

Figure 3. Representative female patient with sleep apnea with reduced [^{18}F]-2-fluoro-2-deoxy-D-glucose uptake in genioglossus in comparison with control female subject on fused positron emission tomography–magnetic resonance images. Note that standardized uptake value (SUV) in genioglossus of the patient with sleep apnea is reduced in comparison with the control subject. AHI = apnea–hypopnea index; BMI = body mass index.

genioglossus (1.25 ± 0.21 vs. 1.37 ± 0.30; $P = 0.046$), between patients with sleep apnea and control subjects after covariate adjustments. No differences between patients with OSA and control subjects were observed for the SUV of the masseter, pterygoid, neck fat, or submental fat (Table 2).

The region of interest used to measure genioglossus SUV was not inclusive of the whole tongue, but rather specifically located at the core position of the genioglossus. Because tongue fat is not homogeneously distributed throughout the tongue, the tongue was subdivided into eight equal sections and intramuscular fat percentage was calculated within each section. Figure 4 indicates that the genioglossus region of interest used to calculate the SUV mainly included the lower RP, upper RG, and upper mid RG regions of the tongue. Because tongue fat percentage could affect the genioglossus SUV, we performed a similar analysis controlling for tongue fat (Table 3) within a subset of the overall sample (for demographic info, *see* Table E1). After additional adjustment for tongue fat in these regions of the tongue, patients with OSA still had significantly reduced FDG uptake in the genioglossus (both overall [$P = 0.023$] and for the middle slice only [$P = 0.032$]) in comparison with control subjects (Table 3). These data indicate that tongue fat is not the main factor mediating decreased metabolic activity in the genioglossus of patients with sleep apnea.

Finally, to further control for differences in covariates, we performed an analysis within 20 case-control pairs (*see* Tables E2 and E3) matched on race, sex, age (within 10 yr), and BMI (within 5 kg/m^2). After matching, the cases and control subjects no longer differed in terms of BMI (37.0 ± 6.9 vs. 36.6 ± 6.9; $P = 0.549$), but cases were still older than control subjects (46.5 ± 10.8 vs. 42.6 ± 11.5; $P = 0.003$) (*see* Table E3). The mean SUV of the tongue was lower in patients with OSA compared with control subjects (1.29 ± 0.24 vs. 1.41 ± 0.29; $P = 0.282$), as in the overall sample. Although this result was no longer significant in our smaller matched sample, where there was reduced power, the magnitude of the difference is identical to that seen in the overall sample. This suggests that the observed effect in our primary analysis was not driven by differences in the covariates.

Correlations between obesity, tongue fat percentage, and SUV of upper airway structures. We assessed whether there was a relationship between obesity (as measured by BMI) and tongue fat percentage and the SUV for each of the upper airway structures (*see* Table E4). We observed significant positive correlations between BMI and SUV in both the masseter (rho = 0.41; $P < 0.0001$) and pterygoid (rho = 0.39; $P = 0.0001$) muscles. There were no correlations seen between BMI and SUV for the other structures. There were no significant correlations between BMI or tongue fat percentages and SUV in the genioglossus, suggesting that obesity plays a limited role in determining the tongue SUV.

Differences in SUV between different upper airway muscles and structures. To assess whether there was evidence of a tissue-specific SUV profile within our sample, we compared the SUVs across the different upper airway structures (Table 2). We observed significant differences in SUV among the structures ($P < 0.0001$) in the overall study sample. In pairwise comparisons, the SUV of the genioglossus (both overall and for the middle slice only) was significantly greater than both the control muscles (masseter and pterygoid) and subcutaneous (neck and submental) fat deposit SUVs ($P < 0.001$ for all comparisons). Similarly, the SUV in the control muscles was significantly larger than that in the fat deposits ($P < 0.001$).

Table 2: Comparison of Soft Tissue SUVs in Case and Control Subjects

	Patients with Sleep Apnea (*n* = 72)	Control Subjects (*n* = 30)	*P* Value*	*P* Value†
Primary soft tissue SUVs				
Genioglossus (middle slice only)	1.25 ± 0.21	1.37 ± 0.30	0.0645	**0.0459**
Genioglossus	1.28 ± 0.20	1.41 ± 0.31	**0.0482**	**0.0296**
Control muscle SUVs				
Masseter	1.01 ± 0.16	0.92 ± 0.24	0.0773	0.3813
Pterygoid	1.14 ± 0.23	1.06 ± 0.23	0.1392	0.6962
Subcutaneous fat deposits SUVs				
Neck fat	0.43 ± 0.19	0.40 ± 0.19	0.4861	0.4362
Submental fat	0.51 ± 0.20	0.50 ± 0.25	0.8047	0.9510

Definition of abbreviation: SUV = standardized uptake value.
Significant differences ($P < 0.05$) are presented in bold.
*P value from t test.
†P value from linear regression model adjusted for age, body mass index, sex, and race.

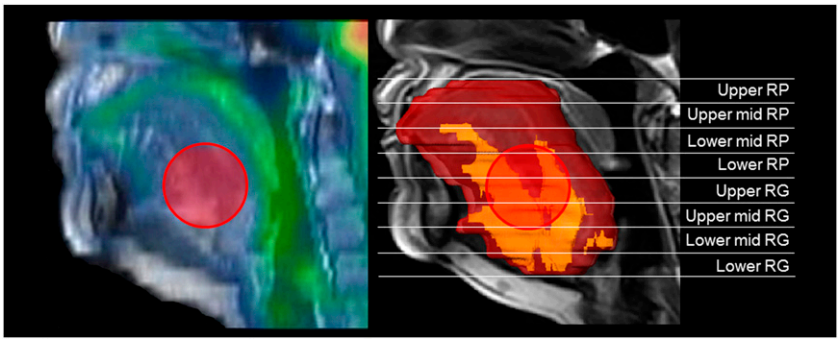

Figure 4. Midsagittal fused positron emission tomography–magnetic resonance images (*left*) and magnetic resonance (*right*) image with volumetric reconstruction of the tongue (*red*) and fat contained within the tongue (*yellow*). The region of interest (*red circle*) from which we measured the standardized uptake value of genioglossus (*left*) is shown in both images and mainly occupies lower retropalatal (RP), upper retroglossal (RG), and upper mid RG regions of tongue. Note that there is significantly more fat at base of tongue (upper RG and upper mid RG) as seen on these positron emission tomography–magnetic resonance images than in upper region of tongue (lower RP).

We also observed significant differences between the control muscle SUVs, the masseter had a lower SUV than the pterygoid ($P < 0.001$), and between the fat deposit SUVs, neck fat had a lower SUV than submental fat ($P = 0.001$). The SUVs for the two genioglossus measures were not significantly different. A similar tissue-specific SUV profile was seen in cases and control subjects separately, indicating that these differences among structures were not dependent on case-control status.

Discussion

This is the first study to implement FDG-PET to examine the metabolic activity of the genioglossus in obese patients with sleep apnea and obese control subjects. After adjusting for age, BMI, sex, and race, we found the following: (*1*) FDG uptake is reduced in the genioglossus of patients with OSA compared with control subjects, (*2*) these results remained after adjusting for tongue fat, and (*3*) there were no differences in FDG uptake in the masseter and pterygoid muscles and in the fat deposits in the neck between patients with sleep apnea and control subjects. These findings indicate that there are selective alterations in glucose metabolism within the primary soft tissue structures of the upper airway in patients with OSA. These alterations may not only be the result of repeated obstructive events, but may also directly contribute to OSA.

Limitations

See the online supplement for more information.

Comparison of Metabolic Activity with that Reported in Previous Studies

FDG-PET scans accurately measure glucose metabolism in healthy tissues (muscle activity) and those with abnormalities (infection, tumor) (33–35). Previous studies using FDG-PET for evaluation of the upper airway have only been conducted in normal subjects. They have shown the distribution of physiologic FDG uptake in the soft tissues surrounding the upper airway in normal subjects, including the genioglossus (31, 32). We found similar SUVs for the genioglossus in our control subjects in comparison with those reported in these previous studies (31, 32). Our reported SUVs for subcutaneous fat deposits (neck and submental fat) are also very similar to those reported in a previous FDG-PET study (30). Therefore, our reported SUVs are within the expected range in our control subjects. There are few clinical examples of abnormally decreased FDG accumulation but FDG activity is reduced in vocal cord paralysis (42–44) in addition to the genioglossus in patients with OSA.

Studies indicate (45–49) that the metabolic activity of skeletal muscle can be imaged and quantified *in vivo* using molecular imaging with FDG and PET. Specifically in the Goncalves paper,

Table 3: Comparison of Soft Tissue SUVs in Case and Control Subjects with Tongue Fat Data

	Patients with Sleep Apnea (*n = 51*)	Control Subjects (*n = 26*)	*P* Value*	*P* Value†	*P* Value‡
Primary soft tissue SUVs					
Genioglossus (middle slice only)	1.26 ± 0.22	1.39 ± 0.31	**0.0404**	**0.0205**	**0.0322**
Genioglossus	1.28 ± 0.22	1.42 ± 0.32	0.0546	**0.0153**	**0.0229**
Control muscle SUVs					
Masseter	1.02 ± 0.16	0.91 ± 0.24	**0.0447**	0.2124	0.1798
Pterygoid	1.14 ± 0.24	1.07 ± 0.24	0.2365	0.6268	0.7086
Subcutaneous fat deposits SUVs					
Neck fat	0.44 ± 0.19	0.40 ± 0.19	0.4149	0.5845	0.5333
Submental fat	0.52 ± 0.21	0.52 ± 0.25	0.9536	0.9748	0.9070

Definition of abbreviation: SUV = standardized uptake value.
Significant differences ($P < 0.05$) are presented in bold.
*P value from t test.
†P value from linear regression adjusted for age, body mass index, sex, and race.
‡P value from linear regression adjusted for age, body mass index, sex, race, and fat percentage in the lower retropalatal, upper retroglossal, and upper mid retroglossal regions of the tongue.

dacarbazine chemotherapy led to decreased muscle metabolism (i.e., decreased FDG uptake), whereas temozolomide chemotherapy led to increased muscle metabolism (i.e., increased FDG uptake) in patients with melanoma. The data from the Goncalves paper showed that normal muscles in the body may have different baseline levels of FDG uptake. In addition, our data did not find significant differences between subjects with apnea and control subjects FDG uptake in upper airway control muscles (masseter, pterygoid) in the neck, whereas there were significant differences in the FDG uptake of the genioglossus. This indicates that FDG uptake differentially affects particular muscles in patients with OSA. This is unlikely to be caused by a systematic error, which would cause all muscles and tissues to decrease in metabolism, not just some of them.

Why Is the Metabolic Activity of the Genioglossus Reduced in Patients with Sleep Apnea?

There are several factors that can explain why the metabolic uptake of glucose in the tongue is reduced in patients with sleep apnea compared with control subjects. Such factors include muscle fiber type that can change with intermittent hypoxia, denervation of the muscle fibers, changes in blood flow, inflammation, and direct fat infiltration in the muscle. Inflammation would be expected to increase the SUV, and studies (50, 51) have indicated that there is greater inflammation in the upper airway of patients with OSA compared with control subjects. Therefore, we do not believe inflammation is the mechanism by which the tongue SUV is reduced in our study.

In patients with OSA, the genioglossus is subject to mechanical disturbances during episodes of pharyngeal airway occlusion. These mechanical disturbances, in the form of muscle contractions, occur at the terminal phase of each occlusive event, and may induce structural damage (13, 52) and muscle remodeling (53). Studies investigating muscle fiber composition have shown that patients with sleep apnea undergo muscle fiber transformations resulting in a higher percentage of type II fibers in the genioglossus (13, 24). Type II muscle fibers have less GLUT-4 content and less hexokinase activity, which both contribute to lowered glucose uptake (20–23) and could contribute to a reduction in SUV of the tongue. Carrera and coworkers (54) showed that continuous positive airway pressure normalizes the type II fiber abnormalities present in OSA sleep apnea. Chronic intermittent hypoxia in animal models has also resulted in genioglossus fiber-type changes in some (55, 56) but not all studies (57, 58). Chronic episodic hypercapnic hypoxia in rats (55) resulted in a reduction in geniohyoid type 1 fibers and an increase in type 2B fibers. In McGuire's study, there was an increase in geniohyoid fatigability consistent with the reduction in fatigue-resistant geniohyoid type 1 fibers and an increase in the fatigable type 2B geniohyoid fibers (55). In a study by Pae and coworkers (56), 10 hours of intermittent hypoxia were shown to induce fiber-type transitions from type 2A to type 2B in the geniohyoid muscle of rats, which persisted for 30 hours. Our data showing a reduced SUV in the tongue in patients with sleep apnea is consistent with an increase in type 2 genioglossus fibers, potentially leading to increased tongue fatigue and an increased likelihood of upper airway collapse or narrowing resulting in apneic events.

Additionally, increased fat deposition in the tongue (27–29) might also play a role in the SUV reduction. The metabolic activity of fat is lower than that of muscle. However, it should be noted that brown fat shows increased FDG uptake (59–61), although brown fat is not thought to be present in the tongue. In our current study, the mean SUVs of the fat deposits in the neck and submental regions were significantly lower than the measured SUVs of the upper airway muscles. Therefore, increased fat within the genioglossus could contribute to lowered FDG uptake within these tissues. However, our data showed a reduction in genioglossal SUV even after controlling for direct measures of tongue fat, which is increased in patients with OSA. Moreover, there was no correlation between the tongue SUV and either BMI or percentage of tongue fat. Thus, we do not believe that tongue fat explains the reduction in the metabolic activity of the tongue.

Recent studies have also shown altered sensory and motor function in patients with OSA resulting in chronic denervation (17, 62). In fact, the elevated EMG in the upper airway muscles in patients with OSA may be secondary to neurogenic remodeling. This can be thought of as chronic partial denervation of muscle fibers, with reinnervation of the muscle fibers by collateral surviving motor axons (14, 63). Such damage to the tongue would result in a reduction in glucose metabolism (18).

It has been proposed that the increased activation of tongue (increased EMG) during wakefulness compensates for narrowing of the upper airway in patients with sleep apnea and is secondary to neuromuscular compensation (7–9). If increases in the tongue EMG activity during wakefulness were secondary to neuromuscular compensation, the SUV of the tongue would be increased. Our data, showing reduced glucose uptake in the tongue, argue against the neuromuscular compensation hypothesis explaining the increase in tongue EMG activity in patients with OSA. Instead, they support the concept that increased EMG activity of the tongue results from denervation-reinnervation injury.

It has previously been suggested that the "enhanced" genioglossus activity in patients with sleep apnea could also relate to central plasticity or facilitation of cranial motor flow to the upper airway muscles (64–66), but this would be expected to increase glucose uptake, whereas our data illustrate that glucose uptake is decreased in patients with OSA compared with control subjects. Our results are more consistent with the denervation-reinnervation hypothesis for genioglossus activity rather than central plasticity or facilitation of cranial motor flow. Apneic events and snoring lead to denervation with subsequent reinnervation of upper airway muscle fibers (13, 14). Reinnervation leads to an increase in amplitude of action potentials of reinnervated muscle fibers (15). Recent data, examining genioglossus activity of individual muscle fibers, indicate that the amplitude of action potentials are, in fact, increased in the tongue of patients with sleep apnea compared with control subjects (10, 16, 17). Denervation would be expected to decrease rather than increase metabolic activity of the tongue, which is consistent with our findings. Finally, there may be other reasons why glucose uptake is reduced in the tongue of patients with OSA compared with control subjects. It is possible that denervation supersensitivity (to acetylcholine) could

occur for tongue EMG characteristics, as studies have shown (16, 65, 67, 68), and the neural drive to the musculature could be diminished across all states from central sources (69). Thus, although we showed that tongue metabolic activity is reduced in patients with sleep apnea there are many possible explanations for this finding.

It is generally regarded that increased neuromuscular drive and EMG activity are sufficient to maintain a patent upper airway during wakefulness (9). However, we believe there is a sleep-related decrement in this normal drive that predisposes the anatomically narrow upper airway to collapse (i.e., it is not the loss of an exaggerated drive) (9). But if glucose uptake (and muscle function) is altered or impaired in the tongue of patients with OSA, and neural drive is "normal," how is upper airway patency preserved during wakefulness? Given our findings that the metabolic activity of the tongue is reduced during wakefulness, it is likely tongue function is abnormal in patients with sleep apnea. However, the tongue is only one anatomic structure mediating upper airway caliber; there are several other soft tissue structures, including the soft palate and lateral walls, which help determine airway caliber. We do not know the glucose uptake of these other structures. Thus, although tongue metabolic activity is reduced during wakefulness, this does not seem to be sufficient to collapse the upper airway during wakefulness or sleep.

In conclusion, we developed a novel paradigm for quantitatively assessing metabolic differences in glucose uptake in the soft tissue structures of the upper airway in patients with OSA. Using FDG-PET, we demonstrated that the tongue in patients with OSA has significantly less glucose metabolism, independent of age, BMI, race, sex, and tongue fat percentage, when compared with obese control subjects. We showed that after adjustment for the amount of fat in the tongue, FDG-PET was capable of identifying significant reductions in glucose uptake in the genioglossus of patients with OSA in comparison with control subjects. Our results support the concept that the increased compound tongue EMG activity in patients with sleep apnea is the result of denervation-reinnervation injury and not the neuromuscular compensation hypothesis. ■

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